Modulation of cognition and behavior in aged animals: role for antioxidant- and essential fatty acid–rich plant foods[1–4]

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ABSTRACT

Aging results in the development of cognitive and motor deficits in humans and animals that are evident by midlife. These deficits are thought to stem from neuronal damage and dysfunction as a result of a variety of stressors, including increased oxidative stress and modifications in brain lipid composition. Recent clinical and animal studies have identified nutritional intervention as a viable method to curtail the cognitive aging process. Human studies have been primarily observational and have indicated that inclusion of antioxidant-rich foods in the diet can slow the progression of cognitive decline. Basic science studies investigating nutritional modulation of age-related cognitive decline have focused on foods rich in antioxidants or essential fatty acids. The purpose of this review is to discuss recent advancements in animal research showing that age-related cognitive and behavioral decline can be ameliorated with nutritional supplementation with polyphenol- or polyunsaturated fatty acid–rich plant foods. *Am J Clin Nutr* 2009;89(suppl):1602S–6S.

INTRODUCTION

Loss of cognitive abilities during aging is a complex process that starts to become evident during middle age in humans (35–65 y old) and rats (12–24 mo old) even in the absence of specific neurodegenerative disease (1). The aged brain exhibits a number of alterations in structure and function, leading to a decline in cognitive and motor abilities. Two hallmarks of the aged brain which have proven amenable to nutritional intervention are oxidative stress and polyunsaturated fatty acid (PUFA) dysregulation (2). Although cells routinely produce reactive oxygen species as a byproduct of normal respiration, cellular production surpasses endogenous antioxidant defenses in the aged brain (3), leading to an increase in oxidative damage to proteins, DNA, and lipids (4). Lipid peroxidation is particularly toxic to neurons because it alters cell membrane properties as well as the function of membrane-bound receptors, ion channels, and signaling molecules (5).

Most fatty acids enriched in neuronal membranes are essential fatty acids, so called because they cannot be synthesized in vivo and must be obtained from the diet. In animals, the aged brain exhibits lower concentrations of PUFAs in neuronal membranes than that of young animals (6). Less phospholipid-bound fatty acid is found in the aged brain, particularly in the cortex and hippocampus (7). These alterations contribute to a decrease in membrane fluidity, which is exacerbated in the hippocampus, cortex, cerebellum, and striatum of aged rats (8). In addition, with less membrane-bound fatty acids available for cleavage, less free fatty acid is liberated from cellular stores to participate in cell signaling cascades. The age-related decline in neuronal membrane fatty acid composition therefore contributes not only to membrane fluidity (9) but also to alterations in neuronal structure and reduced synaptic plasticity (10). For these reasons, recent nutritional interventions have focused on supplementation with foods high in antioxidants or essential fatty acids to prevent neuronal dysfunction during aging. Although several clinical studies have started to show a significant effect of diet on forestalling cognitive decline, most nutritional studies were accomplished with the use of animal models. The use of animals has enabled an exploration of the cellular mechanisms behind nutrition-related cognitive improvement, and recent advances in animal research are the primary foci of the current review.

ANTIOXIDANTS AND COGNITION: ANIMAL STUDIES

The restorative effects of flavonoid-rich foods on age-related cognitive and motor dysfunctions have been repeatedly shown with blueberries (11), strawberries (12), Concord grapes (13), and polyphenols from red wine (14). Initial studies showed that long-term (from age 6 to 15 mo in F344 rats) feeding with a diet supplemented with strawberries, spinach, or vitamin E prevented age-related decrements in cognitive function as assessed by the Morris water maze (12). A subsequent experiment showed that dietary supplementation with spinach, strawberries, or blueberries could actually reverse already established deficits in behavioral and cognitive function in aged (19 mo) F344 rats (11).

In addition, blueberry supplementation of aged animals at 2% of the diet (≈½ cup/d equivalent for humans) was found to improve performance in the radial arm water maze, the Morris water maze, a step-down inhibitory avoidance task, and a foot-shock–motivated 14-unit T-maze and to reverse cognitive declines in object recognition tests (15). Interestingly, blueberry

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and strawberry supplementation had differential effects on Morris water maze performance of young animals exposed to ^{56}Fe irradiation, a model of aging resulting in the deterioration of motor and cognitive abilities. Blueberry supplementation prevented deficits in reversal learning, which depends on intact striatal functioning, whereas strawberry supplementation primarily appeared to affect cognitive processes that depend on hippocampal function (16). Different foods may therefore have distinct functions in the aged brain: rather than improving general antioxidant status to the brain as a whole, individual components from different sources could exert site-specific actions within brain structures governing motor and cognitive functions.

Other polyphenol-rich berry fruit that showed an effect on cognitive function during aging include grapes and red wine (17). The red wine polyphenol resveratrol was shown to prevent cognitive impairment on passive avoidance paradigms, the elevated plus maze, and closed field activity tests (18). In addition, resveratrol administration improved maze performance and locomotor activity in an animal model of Huntington's disease (19) and prevented behavioral decrements seen with chronic ethanol consumption (20). Polyphenols from grape seeds and juice have were also shown to mediate cognitive behavioral performance, improving memory performance in aged (21) and estrogen-depleted spontaneously hypertensive (22) rats. In addition, supplementation of aged rats with Concord grape juice not only improved Morris water maze performance but also motor ability as assessed by the rod walk, wire suspension, and small plank motor tests (13).

In the case of motor function, supplementation with flavonoid-rich foods was shown to improve performance on tests that assess balance and coordination. In the accelerating rotarod and rod walking tests of motor function, blueberry supplementation improved the performance of aged animals, whereas animals supplemented with spinach did not exhibit behavioral improvements on these tests (11). In fact, deteriorations in motor function have proven more resistant to nutritional manipulation than deteriorations in cognitive function. So far, only dietary supplementation with blueberry (11, 15), cranberry (23), strawberry (24), or Concord grape juice (13) was shown to reverse age-related motor behavioral deficits. Interestingly, in the aforementioned studies, the antioxidant activity of many of the experimental diets was equalized, showing that antioxidant activity alone could not predict the efficacy of nutritional interventions in affecting motor function (11). Instead, polyphenolic content is now thought to outweigh antioxidant activity as a determinant of neuroprotective potential of foods. Fruit and vegetables synthesize a vast array of polyphenolic phytochemicals that, although not involved in their primary metabolism, are important in serving a variety of ecologic functions that enhance the plant's survivability. Polyphenols include phenolic acids, stilbenes, coumarins, tannins, and flavonoids. Polyphenolic compounds were recognized to possess many biological properties, including antioxidant, antiallergic, antiinflammatory, antiviral, antiproliferative, antitumorigenic, antianxiety, and anticarcinogenic activities (25).

Studies have suggested that, in addition to having antioxidant and antiinflammatory effects, other positive effects of polyphenolic consumption include direct effects on signaling to enhance neuronal communication, the ability to buffer against excess calcium, enhancement of neuroprotective adaptations, and reduction of stress signals (15). Measures of hippocampal plasticity, including neurogenesis, were also enhanced in rats on a blueberry-enriched diet (26). In addition, extracellular signal-regulated kinase activation and insulin-like growth factor I were increased in the supplemented animals, and concentrations of insulin-like growth factor I receptor positively correlated with improvements in spatial memory (26). Additional research indicates that phytochemicals can regulate mitogen-activated protein (MAP) kinase and other signaling pathways at the level of transcription (27). Given the involvement of mitogen-activated protein kinases in diverse forms of memory (28), these findings suggest that the putative signal-modifying properties of polyphenols may significantly contribute to the cognitive and behavioral improvement. Therefore, it appears from these studies and others that at least part of the beneficial effects of polyphenolic supplementation on behavior in the aged animals may involve enhancements of cell signaling associated with learning and memory.

POLYUNSATURATED FATTY ACIDS AND COGNITION: ANIMAL STUDIES

In addition to consuming antioxidant-rich fruit and vegetables, consuming monounsaturated fatty acids and PUFAs was shown to slow cognitive decline in animals (29) and in humans (30). Most studies have focused on the n−3 and n−6 (omega-3 and omega-6) PUFAs found in fish and nuts (31). Although fish contain primarily the long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), nuts such as walnuts contain the monounsaturated fatty acid oleic acid (8:1) and the n−6 and n−3 PUFAs linoleic acid (18:2n−6; LA) and α-linolenic acid (18:3n−3; ALA) (32). LA is the precursor to arachidonic acid), and ALA is metabolized to either EPA or docosapentaenoic acid. Although numerous studies have shown that consuming diets deficient in n−3 fatty acids will impair cognitive functioning (33), few intervention studies have shown a positive effect of fish oil, DHA, or EPA on cognitive abilities in aged animals (34).

Aged rats provided a diet supplemented with fish oil did not exhibit improved Morris water maze performance (34). However, rats given diets supplemented with ALA and LA throughout life exhibited an increased life span and improved brightness-discrimination learning ability during senescence (35). ALA and LA were also shown to modulate behavior after dietary intervention: young rats administered ALA and LA at a ratio of ≈1:4 exhibited improved Morris water maze performance (36). Dietary ALA and LA supplementation was also shown to affect learning and memory in the senescence-accelerated mouse, a model of cognitive deterioration that exhibits age-related deficits on behavioral tests (37). Dietary supplementation with oils rich in ALA or LA resulted in improved performance on the Sidman avoidance test and in light-dark discrimination learning in these mice (38). Interestingly, the most effective ratio of ALA to LA in improving cognitive performance was found to be 1:4, and walnuts contain ALA and LA at this ratio (39). According to the US Department of Agriculture National Nutrient Database, walnuts also contain essential fatty acids as well as a number of other potentially neuroprotective constituents, including γ-tocopherol (vitamin E), folate, melatonin, phytosterols, and numerous antioxidant polyphenols (40). Accordingly, recent cognitive and behavioral studies have shown that dietary supplementation of aged

rats with walnuts (at 6% of the diet; approximately equivalent to 1 oz/d for humans) improved motor behavior as well as Morris water maze performance, a test of spatial working memory (41). Note that brain uptake of the 2 main fatty acids in walnuts, ALA and LA, is quite low in the rat, although the metabolites of ALA and LA, specifically DHA, EPA, and arachidonic acid, do become incorporated into neural tissue (42). The mechanism by which ALA and LA supplementation improves behavior and cognition in aged animals remains to be elucidated, but it may lie in the ability of dietary PUFAs to modulate neuronal membrane properties and cell signaling cascades.

The structure of neurons is critical to their function: cells must maintain appropriate electrical gradients across the membrane, anchor receptors and ion channels in position to communicate with other cells, and be able to release and reabsorb unmetabolized neurotransmitters (8). Those properties depend on the fatty acid composition of the neuronal membrane. The fatty acid composition of neuronal membranes declines during aging, but dietary supplementation with essential fatty acids was shown to improve membrane fluidity and PUFA content (9). In addition to affecting membrane biophysical properties, PUFAs in the form of phospholipids in neuronal membranes can also directly participate in signaling cascades to promote neuronal function, synaptic plasticity, and neuroprotection (43). PUFAs were also shown to increase long-term potentiation, which would potentially strengthen synaptic contacts in the aging hippocampus (44), affect gene expression in neural tissue, and influence properties as diverse as synaptic plasticity, signal transduction, and energy metabolism (45).

DIET AND COGNITION: HUMAN STUDIES

Clinical observations have indicated that lifestyle factors can influence the integrity of brain function during aging and have led researchers to investigate the effects of diet on cognitive ability. Those studies were primarily observational, correlating the intake of certain foods or overall dietary patterns to cognitive performance. Some studies have indicated that elderly subjects with adequate cognitive capacity consumed more fish, vitamin-rich vegetables, and fewer sweets than did their cognitively impaired counterparts. In addition, daily consumption of vegetables and fruit and weekly consumption of fish was associated with a decreased risk of dementia (46). Because fruit and vegetables contain a number of potentially neuroprotective substances, subsequent studies focused on identifying which components could be modulating cognitive ability. When cognitive decline was assessed in relation to intake of flavonoids in fruit and vegetables, results indicated that consumption of fruit and vegetables high in flavonoid content was associated with better cognitive function at baseline, as well as an attenuation in cognitive decline after 5 or 10 y (47).

In terms of essential fatty acids, PUFA intake from the diet was associated with a reduced risk of age-related cognitive decline in the Italian Longitudinal Study on Aging (48). The Zutphen Elderly Study also found that consumption of essential fatty acids from fish was associated with attenuated cognitive impairment (49).

Although diet represents one modifiable risk factor in the development of cognitive decline, it must be emphasized that other factors such as exercise, social interaction, mental training, and adequate health care can also affect cognitive status in the elderly, and each of these factors may influence dietary habits. Compared with animal studies, studies involving the human population have been somewhat limited. Most human clinical studies have been observational in nature, and, although some interventional studies have been performed, data are inconsistent about the effect of specific nutritional supplements on cognitive function.

CONCLUSIONS

In short, animal studies using dietary intervention with foods high in antioxidants and PUFAs have shown the positive effect that nutrition can have on cognitive and behavioral abilities during aging. Although the ultimate goal of nutritional neuroscience research is to affect the human clinical population, animal studies have enabled researchers to begin to unravel the physiologic and molecular mechanisms behind the effects of diet on brain function. The maintenance of the translational character of animal research will further facilitate the extrapolation of animal data to the human condition. Thus far, animal studies show that the cellular mechanisms behind nutritional intervention appear to be multidimensional: foods high in antioxidant polyphenols and PUFAs can forestall oxidative damage as well as modulate neuronal cell signaling cascades instrumental in maintaining neuronal function during the aging process, leading to improved cognitive function in the aged population. In terms of human data, observational studies conducted thus far tend to show beneficial effects of polyphenol and PUFA consumption on cognition, although more studies are needed to verify these observations. (Other articles in this supplement to the Journal include references 50–76.)

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